U.S. Patent 6,387,624 (Fu et al.) relates to the use of improved poly dT primers comprising two or more variable "V" nucleotides that improve the synthesis of a first cDNA strand from mRNA. These primers are used to synthesize the first cDNA strand (see for example columns 8-9, Example 2) followed by synthesis of a second strand using RNase H activity to generate endogenous RNA primers (see for example column 9, Example 3). This is in sharp contrast to the instant invention where exogenously supplied random primers are used to synthesize second cDNA strands. Accordingly, Applicants do not believe that Fu et al. is relevant to the instant invention. Applicants would like to point out, however, the discussion by Fu et al. (filed April 14, 2000) of two methods to synthesize the second strand of a cDNA molecule from an mRNA template (column 1, lines 40-62). The methods are referred to as "replacement synthesis" (using RNAse H activity) and "primed synthesis" (using terminal transferase activity to tail the 3' end of the first cDNA strand followed by the use of a defined primer which hybridizes to the tail). Both of these are in sharp contrast to the methods of the instant invention where random primers are used to synthesize the second cDNA strand.

U.S. Patent 6,509,175 (Fu et al.) relates to the preparation of full length cDNAs by use of an "oligo-dV" primer which hybridizes to the mRNA strand of a hybrid of mRNA and first strand cDNA that is not fully complementary. The "oligo-dV" primer is used for further reverse transcription (see for example column 7, lines 40-57) and not for the synthesis of a second cDNA strand. To the contrary, standard RNase H activity is used to synthesize the second cDNA strand (see for example column 11, line 52, to column 12, line 2). Accordingly, Applicants do not believe that Fu et al. is relevant to the instant invention.

Rejections under 35 U.S.C. § 103(a)

Claims 1-32 were rejected under 35 U.S.C. § 102(e) as allegedly unpatentable over Lin et al. (US 2002/0137709), hereafter Lin et al. (2002) in view of Adams et al. (USP 6,297,365). Applicants have carefully reviewed the statement of the rejection as well as the cited references and respectfully submit that no *prima facie* case of obviousness has been presented. Applicants traverse for the reasons as follows, which begins with a follow up to the discussion during the interview of November 5, 2003 as described above.

With respect to the alleged possibility that the language of claim 1 with respect to "a plurality of second oligonucleotides comprising a random primer region" is found in Example 5, paragraph 0104 of Lin et al. (2002), Applicants respectfully point out that the language in the claim must be construed in a manner consistent with the specification as filed. Applicants respectfully direct the Examiner's attention to page 16, lines 2-5 of the specification which states that a "region" of "a polynucleotide or oligonucleotide is a contiguous sequence of 2 or more bases." This is consistent with the discussion on page 5, lines 13-14, which refers to "second oligonucleotides" as containing primer regions containing or being "random sequences of various lengths"; and on page 13, lines 6-10, which states that "primers may be random such that they contain heterologous sequence."

Therefore, "a random primer region" as recited in claim 1 refers to a "region" of at least 2 bases that is both a primer and random in nature. This is simply not disclosed or suggested by Lin et al. (2002).

With respect to the content of Example 5, paragraph 0104, on page 9 of Lin et al. (2002), a mixture of primers comprising a single variable "N" position between a defined oligo$(dC)_{10}$ primer region and a defined T7 RNA polymerase region is NOT within the scope of "a plurality of second oligonucleotides comprising a random primer region" because "a random primer region" requires more than a single variable base like that disclosed by Lin et al. (2002). Stated differently, the single variable position "N" in the primers of Lin et al. (2002) is **not** a "random primer region" as recited in the instant claims. Similarly, the oligo$(dC)_{10}$-N sequence in Lin et al. (2002)'s primers is **not** a "random primer region" as recited in the instant claims because the sequence is not "random" when only one base of that sequence is variable.

Accordingly, Lin et al. (2002)'s disclosure in Example 5 does not support the position that all elements of the instantly claimed invention are present in a combination of Lin et al. (2002) and Adams et al. Moreover, Applicants wish to point out that claims 6, 7, 12, 13, 23, and 24 are directed to embodiments of the invention wherein the primer region "comprises at least about six random nucleotides", which is not taught or suggested by Lin et al. (2002).

As previously pointed out by Applicants, the statement of the instant rejection appears to be based upon critical misunderstandings of what Lin et al. (2002) disclose. The first

critical misunderstanding is seen in the allegation that Lin et al. (2002) teach the use of random primers to anneal to a first strand cDNA to synthesize a complementary second cDNA strand as required by the instant claims. The statement of the rejection asserts that step (e) of claim 1 on page 12 of Lin et al. (2002) discloses the annealing of first strand cDNA "with a plurality of second oligonucleotides comprising a random primer region to form a population of second complexes". This is in error because no where in claim 1 of Lin et al. (2002) is there any mention of the use of random primers. Moreover, the assertion is incorrect because step (c) in claim 1 of Lin et al. (2002) already describes the generation of a promoter-linked double-stranded nucleic acid molecule from the first cDNA strand. Step (d) in claim 1 of Lin et al. (2002) describes using that double-stranded molecule to synthesize mRNA fragments, and it is these mRNA fragments that are contacted with primers to permit the production of mRNA/cDNA hybrids in step (e). This is clearly not the same as the act of using oligonucleotides comprising a random primer region to produce double stranded cDNA templates as recited in instant claims 1 and 17 (see sections a)iv) and a)v) of each claim).

Another error in the statement of the rejection is the reference to claim 5 of Lin et al. (2002), which relates to step (c) in claim 1 of Lin et al. (2002) and the use of a promoter-linked primer with the first cDNA strand rather than the starting nucleic acid template. Contrary to the allegation in the statement of the rejection, this does not describe either the use of a promoter-linked primer as encompassed by the instant claims or the use of random primers to form double stranded cDNA as encompassed by the instant claims.

Additionally, and contrary to the statement of the rejection, page 3, paragraph 0038 of Lin et al. (2002) does **not** disclose random primers of at least about six nucleotides. That paragraph only mentions that the poly-deoxycytidylate (dC) portion of certain primers can have from about 5 to about 30 dC bases.

Adams et al. do not remedy the above deficiencies of Lin et al. (2002). Adams et al. do not teach the use of random primers to synthesize a duplex cDNA molecule after annealing to a first cDNA strand Additionally, neither reference teaches or suggests the use of exonuclease as recited in section a)iii) of instant claims 1 or 17.

Therefore, no combination of Lin et al. (2002) and Adam et al. is able to teach or suggest all of the limitations of the instantly claimed methods as required by the standard set forth at MPEP 2143.03 and by the cases cited therein. Therefore, and assuming *in arguendo* that motivation to combine these references is present, no combination of these references can lead the artisan of ordinary skill to the instantly claimed invention. Accordingly, Applicants respectfully submit that no *prima facie* case of obviousness has been presented, and this rejection may be properly withdrawn.

Claims 1-32 were rejected under 35 U.S.C. § 102(e) as allegedly unpatentable over Shannon (USP 6,132,997) in view of Adams et al. (USP 6,297,365). Applicants have carefully reviewed the statement of the rejection as well as the cited references and respectfully submit that no *prima facie* case of obviousness has been presented. Applicants traverse for the reasons as follows.

As an initial matter, Applicants note that Shannon fails to disclose any primers like those discussed above with respect to Example 5 of Lin et al. (2002). Instead, Shannon discloses the production of RNA molecules that are antisense relative to a starting mRNA template. The starting template is used with a promoter linked oligo dT primer that contains some variable positions (see column 4, lines 50-63) to produce a promoter linked duplex cDNA molecule that is transcribed into RNA in the presence of a reverse transcriptase that is rendered incapable of RNA-dependent DNA polymerase activity. There is no disclosure of the use of any random primers for the synthesis of the second strand of the duplex cDNA molecule. To the contrary, the synthesis of the second strand is disclosed as using RNase H activity (see column 6, lines 28-49).

The above is consistent with Shannon's Example 1 (columns 9-11), where no random primers are used to produce a second cDNA strand. Instead, a single primer is used to produce a double stranded template. Shannon's Example 2 (columns 11-14) also does not describe using random primers to produce a second cDNA strand (see column 13, lines 17-29). Shannon's Appendix A (columns 17-18) also does not disclose using random primers to

synthesize the second cDNA strand. Instead, RNase H activity is used (see column 15, line 43, and column 17, lines 8-29).

Therefore, and as in the case with Lin et al. (2002) discussed above, Shannon does not disclose all the elements of the claimed invention as required to support an allegation of obviousness. Because the deficiencies of Shannon are not remedied by Adams et al., Applicants respectfully submit that no combination of Shannon and Adam et al. can lead the artisan of ordinary skill to the instantly claimed invention. Accordingly, Applicants respectfully submit that no *prima facie* case of obviousness has been presented, and this rejection may be properly withdrawn.

Claims 1-32 were rejected under 35 U.S.C. § 102(e) as allegedly unpatentable over Lin et al. (US 2003/0022318), hereafter Lin et al. (2003), in view of Adams et al. (USP 6,297,365). Applicants have carefully reviewed the statement of the rejection as well as the cited references and respectfully submit that no *prima facie* case of obviousness has been presented. Applicants traverse for the reasons as follows.

As an initial matter, Applicants note that Lin et al. (2003) fails to disclose any primers like those discussed above with respect to Example 5 of Lin et al. (2002). Instead, Lin et al. (2003) disclose the cloning of full length sequences of gene transcripts by simultaneous use of reverse transcriptase, DNA-dependent DNA polymerase, and RNA polymerase activities in the presence of both a promoter linked primer and another primer (see page 8, paragraphs 0099 to 0105). The disclosure includes an exemplification of this method to produce amplified RNA/DNA products via thermocycling (see page 11, Example 8). These methods are wholly different from the methods of the instantly claimed invention, where the enzymatic activities of Lin et al. (2003) are **not** simultaneously used and primers are **not** simultaneously used.

Therefore, and despite the possibility of using random primers as described by Lin et al. (2003) in Example 8 and at page 8, paragraph 0106, Lin et al. (2003) does not disclose all the elements of the claimed invention as required to support an allegation of obviousness. Because the deficiencies of Lin et al. (2003) are not remedied by Adams et al., Applicants respectfully submit that no combination of Lin et al. (2003) and Adam et al. can lead the artisan